Letters

In September 1983 he stopped eating, was seen to drink water excessively and three days later became confused, incontinent of urine and vomited twice. He developed an axillary temperature of 39.5°C and stupor. The blood pressure was 130/80 mm Hg and there was severe limb and axial rigidity. The serum Na⁺ was 119 mmol/l, K⁺ 2.9 mmol/l, osmolality 257 mOsm/kg, urine Na⁺ 4 mmol/l, osmolality 234 mOsm/kg and arginine vasopressin level 1.4 pmol/l. CSF examination was normal. Intravenous potassium was again infused and fluids restricted. The CK was 6,900 IU/l and WBC 14.8 × 10⁹/l. The following day serum Na⁺ was 126 mmol/l, K⁺ 2.3 mmol/l and urine Na⁺ 101 mmol/l. Four days later the CPK was 15,400 IU/l and after eight days Na⁺ was 138 mmol/l and K⁺ 3.9 mmol/l. At no time had the patient been hyperactive or comatose and there had been no diarrhoea, persistent vomiting or diuretic administration. Blood glucose, renal and thyroid function, synacthen test and chest radiograph were normal. Urinary porphyrins, urine and blood cultures were negative.

An excess frequency of severe hyponatraemia has been reported among schizophrenic patients admitted to hospital.² These patients present in an obtunded state with seizures, vomiting and low plasma and urine osmolalities. Excessive water drinking, anticholinergic therapy and acute psychosis have been considered as possible causes. Neuroleptic drugs are rarely implicated alone, but in such cases are thought to impair water excretion by provoking inappropriate ADH secretion, rather than promoting its effect on the renal tubule.³ In this patient there were a number of possible causes of hyponatraemia, including sodium depletion and excess water drinking. The cause of the hypokalaemia was not established, but adrenergic overactivity could have contributed.

The pathogenesis of neuroleptic malignant syndrome is unknown but it is provoked by drugs with a high incidence of extrapyramidal side-effects. The initiation or alteration of such medication often precedes the syndrome by 5–15 days, but it can occur without obvious trigger after months of treatment. In these circumstances physical exhaustion and dehydration are suggested as initiating factors and water depletion is commonly present (serum Na⁺ 150–155 mmol/l).¹ The association with triggers other than direct drug effects has not been clearly shown. The current view of the aetiology implicates the basal ganglia and hypothalamus in a drug-induced state of dopamine receptor blockade.⁴ Presumably

rigidity with heat generation is of striatal origin and hyperthermia develops as a result of hypothalamic effects. In this case the recurrence of neuroleptic malignant syndrome with hyponatraemia suggests the two disorders were linked. It is feasible that a primary disturbance of water intake or inappropriate antidiuresis is related to the hypothalamic disturbance of the neuroleptic malignant syndrome. Evidence implicating catecholamine mechanisms in the regulation of water balance is incomplete, although dopamine may interact with angiotensin in the control of water intake.⁵ It remains to be seen how this unique case might relate to the pathogenesis of neuroleptic malignant syndrome.

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High plasma osmolality following intravenous dimethylsulphoxide in the treatment of post-operative hemiplegia

Sir: Dimethylsulphoxide has been used in North America to treat a wide variety of disorders.¹ In Britain it has been used topically as a vehicle for drug delivery, for bladder instillation to treat interstitial cystitis and for a number of other disorders including rheumatoid arthritis.² There is evidence that intravenous dimethylsulphoxide is useful in management of post-operative hemiplegia.³ Marked disturbances in serum osmolality

and electrolytes during intravenous dimethylsulphoxide therapy have been reported, each associated with the death of the patient.^{4,5} We report details of a case of post-operative hemiplegia treated with intravenous dimethylsulphoxide where the clinical, pharmacological and biochemical data suggest that the electrolyte disturbances are due to an osmotic diuresis caused by high plasma and urine concentrations of dimethylsulphoxide.

A 33-year-old man underwent a right frontal craniotomy for partial removal of a known craniopharyngioma with suprasellar extension. Eight hours after the operation he developed a right-sided hemiparesis, and his left pupil was fixed and dilated. Intravenous dimethylsulphoxide therapy was commenced. A 40 g loading dose over forty minutes was followed by 3 g/kg/day over a two day period, then 1.5 g/kg/day for four days when the drug was discontinued. Twenty four hours after the operation the patient was alert and conscious but the focal neurological signs remained. He had a high urine output with a low specific gravity and so desamino-arginine vasopressin 1 µg intramuscularly b.d. was commenced (pre-operative assessment had shown normal posterior pituitary function). Haemoglobin was present in the urine. From day five after operation onwards there was a progressive deterioration in consciousness level associated with pyrexia, leucocytosis and a falling haemoglobin concentration. On day seven he developed clinical and radiological signs of chest infection, and despite resuscitative measures, died on the tenth post-operative day. Necropsy revealed bronchopneumonia and pyogenic pericarditis. Dissection of the brain confirmed the presence of a partly removed craniopharyngioma involving the optic chiasma and pituitary stalk. There was an infarct transecting the internal capsule in the right caudate nucleus and ischaemic damage to the basal ganglia.

The table shows the post-operative increase in his measured plasma osmolality. Much of the increased osmolality can be accounted for by the plasma concentration of dimethylsulphoxide and its major metabolite dimethyl sulphone. There was also an increase in calculated osmolality with marked hypernatraemia and high intracellular sodium concentration compatible with water depletion totalling 6.6 litres over seven days. This deficit was in close agreement with the fluid balance charts. Urine output averaged 3130 ml per day over this period. Measured sodium intake and output were roughly equal. The plasma urea concentration increased from 5.1 to

Table Biochemical data from the post-operative period

Days after operation	Measured plasma osmolality (mosm/kg)	Calculated plasma osmolality (mosm/kg)	Plasma DMSO + DMSO ₂ (mmol/l ²)	Extracellular fluid			Intracellular fluid		
				[Na] (mmol/l)	Total Na (mmol)	Volume (litres)	[Na] (mmol/l)	Total Na (mmol)	Volume (litres)
0	—	280	—	134*	1876†	14†	11.0†	308†	28†
4	463*	330	96*	—	—	—	—	—	—
7	444*	343	51*	160*	1876†	11.7† (-2.3)	13.0*	308†	23.7† (-4.3)
10	341*	315	29*	—	—	—	—	—	—

Total H₂O deficit after 7 days = 2.3 + 4.3 = 6.6 litres.

DMSO = dimethylsulphoxide. DMSO₂ = dimethylsulphone.

* = measured value.

† = assumed value for 70 kg man.

‡ = calculated value.

Calculated osmolality = 2 (Na + K) + (glu) + (urea), all in mmol/l.

7.5 mmol/l but the plasma creatinine concentration remained unchanged at 120 µmol/l. The urine concentration of dimethylsulphoxide and dimethylsulphone measured on day seven was 413 mmol/l. The plasma elimination half life of dimethylsulphoxide was 20.5 hours, which is in agreement with that reported by other workers.⁶

The water depletion which this patient suffered was unlikely to be due to cranial diabetes insipidus since adequate intramuscular doses of dDAVP were administered. The most likely mechanism is an osmotic diuresis due to the high plasma and urine concentrations of dimethylsulphoxide and dimethylsulphone. It is likely that the loss of 15% of body water contributed to the deterioration in his level of consciousness. Subsequent patients have received dimethylsulphoxide at a lower dosing regimen (1.5 g/kg over the first eight hours then 0.8 g/kg over the next sixteen hours and 0.5 g/kg every subsequent twelve hours). This produces dimethylsulphoxide levels in the range 25–40 mmol/l and dimethylsulphone in the range of 10–20 mmol/l. This regimen, together with careful attention to fluid balance, has not resulted in any further cases of serious biochemical disturbance. Patients with impaired renal function will require lower doses since 50% of an intravenous dose is excreted unchanged in the urine.

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Possible peripheral neuropathy at high altitude

Sir: Although it is well documented that peripheral neuropathy can be caused by many aetiological factors at normal altitudes cases which accompany high altitude sickness have not been reported or examined to our knowledge.¹ Our Hokkaido University Alpine Club accomplished the first winter ascent in the world of a summit more than 8,000 meters high in 1982. In the preceding decade we had dispatched five expeditions to mountains above 6,000 m for the purpose of scientific research and training in high altitude climbing. Among these five parties, 44 members succeeded in climbing to an altitude over 6,000 meters. However, three climbers suffered from high altitude sickness, two of whom complained of impaired sensation in the distal parts of their four extremities. In this observation we describe the clinical aspects of these two cases and speculate upon the pathophysiological factors.

The first case was a 20-year-old-man, who had not been above 3,000 m before, who underwent ascent training on Mount McKinley, Alaska in 1972. He complained of a headache and general weakness on reaching 5,300 m. His symptoms gradually became worse, so he stayed in camp at 5,300 m for two days, while the other members ascended to the summit. An examination on the evening of the fourth day after the onset of the illness showed drowsiness, slurred speech and truncal ataxia which were so severe that he could not stand still. His lungs were almost normal on auscultation, but nocturnal Cheyne-Stokes respiration was noted. He was treated with acetazolamide and evacuated to 4,000 m with the help of other members. When his consciousness was restored, he noticed the impairment of all sensory modalities in both his hands and feet. The next day he descended to 3,300 m without help, and in four days he made a complete symptomatic recovery. He retained no memory of the fourth day and fifth day of his illness.

The second case was in a winter climbing party which went to Mt Baruntse (7,200 m) in the Nepali Himalaya in 1980. A 24-year-old anaesthetologist then suffered from high altitude sickness. The climb began on 4 November. On the 10th day while crossing a pass at 4,200 m, he experienced severe headache and fatigue. On the 13th day he was cyanotic and walked with difficulty owing to truncal ataxia, but all symptoms disappeared by the 20th day. On 12 December, he climbed again to 6,200 m, and headache and fatigue returned. After two days he was confused and unable to stand by himself. He was carried to 5,100 m, where he recovered consciousness, and noticed sensory loss in both his arms and legs predominantly involving the distal portions of four extremities. He exhibited cen-